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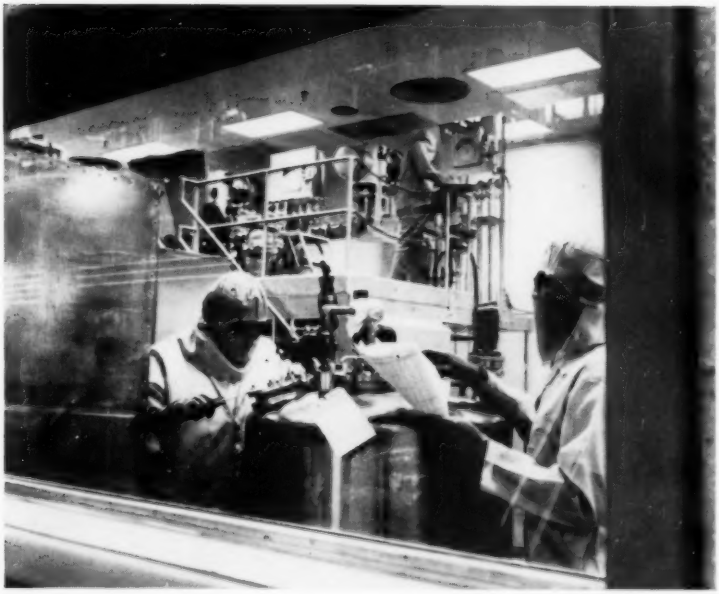

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E D I T O R I A L

STRICTER CONTROLS NEEDED IN THE DISTRIBUTION OF DRUGS

THE over-the-counter sale of prescription drugs by pharmacists is the one evil in the drug distributive picture about which one hears most often, but it is not by any means the only source whereby prescription drugs are distributed illegitimately. The action by the Food and Drug Administration in bringing pharmacists to task who are guilty of selling prescription drugs improperly is entirely appropriate and it is not our intention here to make it appear that these actions should be overlooked nor efforts to prevent them discontinued. It does, however, bother us no end to see how little is done in stopping other equally significant loopholes whereby prescription drugs get into lay hands. Here, we refer to the rather loose policy used by certain manufacturers and drug wholesalers in acknowledging orders for prescription drugs and shipping these to unauthorized persons.

A few drug manufacturers and some wholesalers seem to operate on the premise that, if some corporate body places an order for prescription drugs, they should be privileged to honor this order and ship the drugs in question on the assumption that they will be received and used by a professionally qualified person. Very often, this is not the case, as any careful investigation will bear out. A similar situation exists in regard to small hospitals and nursing homes which do not have a pharmacist on the staff and where drugs are purchased without even the attending physician being aware of the transaction. Here, it should be clearly pointed out that purchasing agents, administrators, plant superintendents, technicians, nurses, and all others who are neither physicians nor pharmacists should not be privileged to purchase prescription drugs. It is also by this very loose process that many drugs—some of them particularly harmful—get into lay hands without bearing a prescription label and without any medical supervision whatsoever being given their administration. Pharmacists have been complaining about this matter for a long time but with rather indifferent success in having this dangerous pro-

cedure stopped. Those who are in a position to do something about it are only too ready and willing to accuse the pharmacist of economic self-interest but it should not take a very careful perusal of the Food, Drug, and Cosmetic Act to determine that it was the intent of Congress when this Act was passed that at no time in the entire distributive pattern for drugs were they to be permitted in lay hands except when labelled as a prescription bearing their physician's name.

There is in progress both at the federal level and in many states some serious effort to amend or alter legislation pertaining to prescription drugs. Among other things, we would strongly urge the following as essential in correcting this evil:

> All drug manufacturers and drug wholesalers involved in any way in the manufacture and distribution of prescription drugs should be licensed by the federal government and by the state or states in which they operate and that, among other things, one of the conditions for issuing such a license would be conformity to a regulation specifically forbidding the sale of prescription drugs except to other licensees; namely, other drug manufacturers and wholesalers, or to pharmacists, physicians, dentists, and veterinarians licensed by the respective state. All others desiring to purchase prescription drugs such as nursing homes, for example, should have their orders honored only if such orders were signed by a duly licensed pharmacist or physician who would then assume the personal responsibility for seeing to it that the drugs were subsequently dispensed according to law.

While not a part of the theme of this editorial, the licensing of drug manufacturers might well also include regular plant inspections by an appropriate agency of federal and state governments to make certain that the drugs were being manufactured under proper conditions and that suitable means of control were available. This would also eliminate another serious problem of which we have had some glowing examples in recent months.

In conclusion, we repeat that it is somewhat incongruous for pharmacists to be cited by the Food and Drug Administration and fined a rather considerable amount for being involved in a process which places prescription drugs in lay hands while little or nothing

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In conclusion, we repeat that it is somewhat incongruous for pharmacists to be cited by the Food and Drug Administration and fined a rather considerable amount for being involved in a process which places prescription drugs in lay hands while little or nothing

is done in correcting this evil in other directions which are equally significant. Prescription drugs should be under rigid distributive control since they are, without question, dangerous except when taken under medical supervision. If this tenet is accepted as it should be then no delay should be made in providing the controls to secure this result.

L. F. Tice

RECENT ADVANCES IN POLIOMYELITIS RESEARCH

By Louis Gershenfeld *

I. *Introduction*

MANY important advances in the field of poliovirus research occurred during the past decade since Dr. John Enders and his coworkers developed the methods to grow polioviruses in tissue cultures (1). Furthermore, these viruses were grown in non-neural embryonic tissues. This discovery, which earlier investigators had mistakenly declared impossible, opened the way for the development and production of poliovirus vaccines.

In 1954, Dr. Jonas Salk and his associates successfully produced and tested a killed poliovirus vaccine in this country (2), which also was adopted by other countries. For the first time, it was possible to protect individuals against this dreaded disease. Although the Salk vaccine presented many problems to manufacturers, public health personnel, and physicians, its efficiency and safety are readily accepted today (3).

The past year has seen two more important advances in polio vaccines. The first is the development of a killed purified polio vaccine by the Merck Sharp and Dohme Co. (4) and, the second, the culmination of many years of research work with the announced success of an attenuated live poliovirus to be administered orally (5).

This presentation considers some of the important problems concerned in this rapidly moving field of poliovirus research.

II. *Present Immunization Practice in this Country and the Effectiveness of Salk Vaccine*

A. *The Increase in Paralytic Polio in 1959 in the U. S.*

The public health epidemiological service has reported that in 1959 there were about twice the number of paralytic polio cases as

* Director, Dept. of Bacteriology, Philadelphia College of Pharmacy and Science, Philadelphia 4, Pennsylvania.

had been reported in 1958. Although three hundred million doses of vaccine had been used in the U. S. since its introduction in 1955, poliomyelitis increased in 1959 instead of disappearing. Three reasons for the failure to eradicate this disease were advanced: (1) failure of the vaccine to protect individuals against paralytic polio; (2) failure to use the vaccine in areas where the disease was prevalent; (3) new virus properties developed among the present poliomyelitis strains, which are not fully understood at present (6).

B. *Polio Pattern in the U. S. in 1959*

Prior to 1954, no class or economic levels were considered in cases of poliomyelitis. Actually the disease was more prevalent among the children of pre-school and school age in the upper economic bracket. In 1959, the disease was seen primarily in sharp local epidemics in the unvaccinated groups. Racial patterns and low living standards appear now to be of prime importance in the epidemiology of the disease. Polio is now observed among Negroes six to fifteen times more frequently than among the white population. The 1952 epidemic in Des Moines, Iowa not only occurred in the slum areas but the number of cases was just as numerous in the suburban sections of the city. In 1959, almost all cases were found in the distressed areas of the town (6).

C. *Effectiveness of the Salk Vaccine*

It was noted in 1959 that 65 per cent of all paralytic polio cases were not vaccinated. Seventeen per cent had received one to two injections. Sixteen per cent received three and two per cent, four injections. The U. S. Public Health Service indicated that the vaccine is 80 to 90 per cent effective and that the continuing development of new vaccine techniques will produce killed polio vaccines of even greater efficiency. The experience of the U. S. P. H. S. is that the yearly outbreaks of paralytic polio in the U. S. are not due to the failure of the vaccine to prevent the disease, but to the lack of using the vaccine among the lower income members of our society.

III. *Development of a Purified, Standardized Polio Vaccine by Merck Sharp and Dohme, Inc. (M. S. D.)* (4, 6)

A. *Differences between M. S. D. Purified Polio Vaccine and Salk Vaccine*

1. The potency can be standardized and made as high as desired.
2. Extraneous monkey kidney proteins are removed and the viruses are purified by enzyme treatment and ultracentrifugation.
3. A new type I strain of virus, Parker, is substituted for the more virulent Mahoney strain.
4. The dose is 0.5 ml. rather than 1 ml., as in the case of the Salk vaccine.
5. Two inoculations appear to give 100 per cent immunity to all three types of polio viruses as compared to three or more doses of the Salk vaccine.

B. *Rough Purification Diagram*

Virus and monkey kidney cells → Seitz filtration → yeast nucleic acid ppt., ppt. then redissolved at pH 7.0 → RNase and DNase enzyme digestion → salt precipitation of impurities → low and high speed centrifugation → formaldehyde inactivation → chemical and physical tests → purified polio vaccine.

1. The complement-fixation test is utilized to test for monkey kidney impurities.
2. Inactivation curves follow a first order reaction, as Salk originally claimed for the first lots of vaccine produced in his laboratories. Viruses (Types 1, 2, and 3) are usually inactivated between 62 and 70 hours.

C. *Serological Conversion*

M. S. D. Polio Vaccine claims better than a 90 per cent antibody conversion (four-fold) after only 2 injections for early lots of purified

polio vaccine (see table below). They now claim about 100 per cent conversion for the latest vaccine lots (4, 6).

Four-Fold Serological Conversion of Killed Polio Vaccines

M. S. D. Purified	*Mahoney*	*Parker*	*MEF-1*	*Saukett*
Polio Vaccine	94%	98%	100%	92%
Salk Polio Vaccine	71%	76%	98%	80%

Brown and Kendrick (7) present data indicating that, in the use of a quadruple vaccine, "the suppressive effect of maternal antibodies affected not only the primary but also the booster response to the several antigenic components; tetanus antibody production seemed to be least influenced." Such injections given to infants from two to four months of age resulted in a "response of the majority of the infants to the poliomyelitis components of the vaccine (which) was definitely poorer than to the diphtheria, tetanus, and pertussis components." They conclude, "In view of the data presented it would seem there should be serious consideration of delaying poliomyelitis vaccination of infants until maternal antibodies are more likely to be gone or at least reduced to a low level."

IV. *Spread of Vaccine Strains of Polio Virus Within Households and Communities*

Dr. John Fox of the Public Health Institute of New York City conducted studies which indicate that the live vaccine strains do not spread as readily as the wild virulent poliovirus strains, and that this spread is far greater among lower income than higher income groups (7). Thus, environment in terms of modern sanitation plays a role in the spread of the vaccine. Very young children disseminate the virus to a greater extent than do adolescents or adults. This probably is due to their close contact at play and in school. Attenuated live type 3 polio vaccine for unknown reasons has been responsible for the greatest degree of virus spread, whereas type 1 causes the least.

Back mutation from the avirulent forms of the virus vaccine strains to more virulent states has occurred, but this degree of reversion to neurovirulence is very mild and appears to be progressive (8).

Interference by other enteroviruses may play an important role in intestinal immunity. Dr. Fox indicates interference is kept at a

minimum when one poliovirus is fed at a time but, when three polio types are fed simultaneously, the interference problem is magnified.

Present epidemiological studies reveal that one cannot depend on virus spread to immunize everyone. Therefore, the vaccine must be fed to the total non-immune population to obtain maximum efficiency.

V. *Dr. Albert Sabin's Field Studies with Live Polio Virus Vaccine and Their Significance for a Program of Ultimate Eradication of the Disease*

In one Russian study, almost one million children, serologically negative for types 1, 2 and 3, received the oral vaccine strains separately. Eight cases of poliomyelitis developed in the test area, but none were attributed to the vaccine. This, according to Dr. Sabin, proves the safety of the oral vaccine. Furthermore, there were no paralytic poliomyelitis cases among contacts of the vaccinated children (9, 10).

In Estonia and Lithuania, which were saturated with the vaccine, there was no rapid summer increase in the number of cases of paralytic polio in 1959, as had been observed in every summer previous to 1959.

The mode of action of the attenuated live oral polio vaccine is first to immunize the intestinal cells making them resistant to infection by virulent strains of the virus. Second, contact immunization from the attenuated live vaccine within families and closely knit social groups helps check the passage and spread of the virulent forms of the virus. Third, antibody formation against polioviruses would check the spread of virulent strains of the virus toward the central nervous system.

A series of interesting experiments conducted in Mexico concerned some of problems of viral interference on the successful immunization with an attenuated live oral polio vaccine. The latter was given at short intervals to children up to ten years of age. A total of 20,000 virus isolations were then carried out to determine the amount of enteric organisms in the intestinal flora of these children (11). After the polio feedings, the polioviruses completely dominated the fecal flora of the experimental groups in the geographic area studied. Later polioviruses disappeared from the stools and the other enteric viruses predominated once again.

The serological conversion rates for the oral vaccine after two feedings of the three viruses were 96 per cent for type 1, 96 per cent for type 2, and 72 per cent for type 3. Dr. Sabin noted that this evidence proves that total mass vaccination during a non-polio season of the year would suddenly break the continuing chain of transmission of virulent polio strains, thereby immunizing (intestinally and humorally) vast numbers of the population in a country.

It appears that, in areas where insanitary and unhygienic conditions prevail, there is a wide dissemination of polio and other enteric viruses, and usually single doses of poliovirus vaccine do not yield the anticipated antibody response that is produced among those in healthier areas. Accordingly, a new schedule of immunization doses is suggested for the insanitary areas, which are usually the regions where most of the world's population is forced to live (9).

VI. *The Use of* In Vitro *Genetic Markers to Determine Reversion to Virulence of the Live Vaccine*

Dr. Joseph Melnick and his co-workers have been studying the properties and behavior of the orally attenuated poliovirus strains. They have found that the Sabin virus strains are superior (better attenuated) by intracerebral and intraspinal inoculations into monkeys as compared to the other types of live poliovirus vaccines. These studies further indicate that type 2 poliovirus is the most attenuated of the three types of viruses (12).

The use of *in vitro* genetic markers to determine reversion to virulence was developed by different virologists who observed that virulent strains of polioviruses can be distinguished from avirulent strains by a series of laboratory "genetic" techniques. These markers are:

1. Plating efficiency under agar medium of low bicarbonate content. The virulent strains, such as Mahoney, grow equally well under acid or alkaline agar overlay and are called d+ viruses. The attenuated viruses grow poorly under acid agar overlay and are known as possessing d− characteristics.

2. Comparative plating efficiency in tissue cultures of fresh primary monkey kidney (MK) and an established serial passed line of monkey kidney known as the MS cells. The virulent strains of polioviruses grow equally well in cultures of the MK

and MS lines and have been classified as possessing MS+ characteristics. The attenuated strains of viruses grow poorly on monolayers of MS tissue cultures and possess MS− characteristics.

3. Growth of virus in tissue culture kept at different temperatures. Strains which paralyze monkeys after intracerebral inoculation are much less sensitive to inhibition by temperatures at 40-41°C. (t+) than are strains which are attenuated for monkeys (t−).

4. Other genetic markers are (a) the elution of virulent strains of polioviruses from cellulose chromatographic columns and (b) the ease of breakthrough against specific antisera by virulent strains in the neutralization plaque technique. These last two markers are still being evaluated in laboratory studies.

Dr. Melnick has observed that an appreciable number of virus isolations from children fed oral vaccine changed from d− to d+ and from t− to t+. Vaccine strains (d−t−) which were negative after intracerebral inoculation of monkeys with $10^7 TCD_{50}$ of virus now produced paralysis after intercerebral inoculation following human passage. Paralysis due to intraspinal inoculation of the oral vaccine in monkeys which had required $10^4 TCD_{50}$ to paralyze 50 per cent of the animals now required only 10 TCD_{50} of virus from post human feeding to produce paralysis. Two d+ t+ strains were also tested in chimpanzees and both produced paralysis, in contrast to the avirulence exhibited by the d−t− vaccines in this primate. It is possible to show increased monkey neurovirulence by intramuscular inoculation as well as the intraspinal and intracerebral methods. As little as a 100 TCD_{50} of human oral vaccine injected I. M. was able to produce paralysis in monkeys.

VII. *What Must be Accomplished Before Licensing of Attenuated Live Virus Polio Vaccine*

Oral live polio vaccine is a radical deviation from the normal prophylactic vaccines which the Division of Biologic Standards (N. I. H.) is accustomed to dealing with at this time. Therefore, much careful accumulation of scientific data must be collected and

properly evaluated before licenses for manufacturing can be issued. Dr. Sabin's data cannot be used by a manufacturer for licensing data. Furthermore, a great deal of information would have to be collected by a producer before the vaccine could be placed on the market (13).

A. *Safety Factors*

Attenuated live polio vaccine reproduces and multiples in the intestinal cells and, since this is a new departure in vaccines, it will be necessary for the manufacturers to collect a large amount of data concerning vaccine spread to unvaccinated contacts. It will be mandatory not only to guarantee the safety of the inoculated individual, but also his contacts, as to the innocuousness of the seed virus and also the absence of contaminating viruses.

B. *Potency*

The attenuated live polio vaccine must be able to produce the desired effect (antibody rise) with regard to effective immunization within a proper dosage range. This immunization data must be submitted together with the manufacturer's claims of efficacy.

C. *Vaccine Criteria to Be Met for Licensing*

1. The manufacturer must possess intimate knowledge of the history and established properties of the live poliovirus strains in his vaccine and be able to present full documentation on this information.
2. The vaccine strains cannot show neurovirulence in monkeys by intracerebral and intraspinal inoculations.
3. The problem of viremia in man must be studied and the results presented with the other pertinent data presented for licensing. The Division of Biologic Standards of the National Institutes of Health (N. I. H.) has not set a permissible viremia level at this date.
4. Genetic stability of the vaccine strains must be proven. The absence of significant neurovirulent reversion must be guaranteed.

5. Field studies requiring at least 100,000 triple negative individuals must be studied. These individuals must be examined serologically for all three polio types.
6. An antibody rise in at least 90 per cent of the susceptible individuals must be demonstrated to show the potency of the vaccine.

D. *Extraneous Tests and Information Required*

1. The live polio vaccine must be produced in monkey kidney cells and not more than three virus passages from the seed can be used in the vaccine.
2. Very rigid exclusion tests must be conducted to eliminate poxviruses, ECHO, Coxsackie, B virus, LCM, tubercle bacilli and other possible contaminants. Laboratory personnel must be strictly isolated from other laboratory workers and should be vaccinated against many of the viruses and bacteria that might be a hazard in this work.

E. *Rigorous Stability Studies with the Vaccine Must Be Carried Out*

1. Much information must be collected concerning the degree of stability of the various vaccine strains at different temperatures over long periods of time.
2. The effect of prolonged storage on the antigenicity of the vaccine must be determined accurately.

It is, therefore, apparent that the Division of Biologic Standards of the N. I. H., United States Public Health Service will only issue a license for the manufacture of attenuated live poliovirus vaccine when it is firmly convinced that the vaccine manufacturer has repeatedly met the severe criteria created for the production of this vaccine and that the interests of the general public will be carefully protected with regard to safety and efficacy of the vaccine.

VIII. *Present Status of Immunization Against Poliomyelitis*

In view of the numerous problems associated with the development, manufacture, and commercial production of an attenuated live

orally administered vaccine, it is doubtful whether substantial supplies of the latter can be made available before the 1961 polio season, though the N. I. H. has approved licensure for the Sabin polio vaccine. It is impossible, at this time, to give a specific date when approved oral polio vaccine will be marketed. However, it is of paramount importance to note that, until such time, wider use of inactivated polio vaccine (either Salk Vaccine or M. S. D. Vaccine) should be practiced in this country to bring about reductions in the incidence of poliomyelitis. When attenuated live poliovirus vaccine will be available, its use will be more effective on a community rather than on an individual basis. Many problems will arise which will have to be solved. Among them are: methods of administration, special groups first to be immunized, program planning and its continuation for such period of time as found necessary to achieve and maintain the maximum results, etc.

IX. *Miscellaneous*

Hiatt (14) presents data concerning the selective photodynamic inactivation of contaminating viruses in live poliovirus preparations, thus making available "a feasible process that may find a useful application in the manufacture of live poliovirus vaccine."

Evans (15) delivered the Presidential Address on "Factors Influencing Illness in Poliomyelitis" at the 1960 Annual Meeting of the Society of American Bacteriologists. Therein is to be found "an analysis of factors that influence the course of a primary poliovirus infection in an unvaccinated individual."

REFERENCES

(1) Enders, J. F., Weller, T. H, and Robbins, C. F., "Cultivation of the Lansing Strain of Poliomyelitis Virus in Cultures of Various Human Embryonic Tissues," *Science, 109:*85-87 (1949).

(2) Salk, J. E., "Recent Studies on Immunization Against Poliomyelitis," *Pediatrics, 12:*471-482 (1953).

(3) Francis, T. F., Jr., and Korns, R. F., "Evaluation of 1954 Field Trial of Poliomyelitis Vaccine: Synopsis of Summary Report," *Amer. J. Med. Science, 229:*603-612 (1955).

(4) Hilleman, M. R., Charney, J., and Tytell, A., "Development of a Purified, Standardized Polio Vaccine," Symposium on Polio Vaccines. The Academy of Medicine of New Jersey, April 20, 1960.

(5) Papers and discussions included in Pan. Am. San. Bur. Scientific Publ. No. 44 (Live Poliovirus Vaccines), 1959.

(6) The 5th International Poliomyelitis Conference, Copenhagen, July 26-28, 1960.

(7) Brown, G. C., and Kendrick, P. L., *J. A. P. H. A., 50:*1529-1538 (1960).

(8) Gelfond, H. M., Potash, L., LeBlanc, D. R., and Fox, J. P., "Revised Preliminary Report on the Louisiana Observation of the Natural Spread Within Families of Living Vaccine Strains of Poliovirus," Pan. Am. San. Bur. Scientific Publ. No. 44 (Live Poliovirus Vaccines), 1959, pp. 203-217.

(9) Sabin, A. B., "Recent Studies and Field Tests With a Live Attenuated Poliovirus Vaccine," *ibid.,* pp. 14-33.

(10) Sabin, A., "Live Poliovirus Vaccine," *WHO Chronicle, 14:*137-142 (1960).

(11) Sabin, A. B., *et al.,* "Live Orally Given Poliovirus Vaccine," *Jour. Amer. Med. Assoc., 173:* 1521 (1960).

(12) Melnick, J. L., "Problems Associated With the Use of Live Poliovirus Vaccine," *Jour. Amer. Public Health Assoc., 50:*1013-1031 (1960).

(13) Murray, R., Symposium on Polio Vaccines. The Academy of Medicine of New Jersey, April 20, 1960.

(14) Hiatt, C. W., "Photodynamic Inactivation of Viruses," *Trans. N. Y. Acad. Sci.,* Ser. II, *23,* 66-79 (1960).

(15) Evans, Charles A., "Factors Influencing the Occurrence of Illness During Naturally Acquired Poliomyelitis Virus Infections," *Bacteriological Reviews, 24,* 34-352 (1960).

ATHEROSCLEROSIS AND HYPERTENSION

By Thomas H. F. Smith *

THE relationship between hypertension and atherosclerosis constitutes the basis of an argument of long standing. It originated many years ago and has tenaciously resisted all attempts to resolve the problem.

Harvey (1) mentioned in 1628 an observation of the ". . . difficulty of transmission of the pulsific faculty" in a patient whose arteries he later observed at autopsy and found to be thickened and calcareous. Harvey knew nothing of hypertension at this time.

The concept that elevated blood pressure might originate from abnormal tensions in the arterial system was first conceived by Traube (2), in 1856, and Kirkes (3), in 1857, each working independently. Traube questioned the fact that arteriosclerosis and cardiac hypertrophy were the coordinated consequences of a primary increase of blood pressure, and concluded that a reverse situation was the case. In 1872, Gull and Sutton (4) described a "hyaline fibroid" change of the arterioles and capillaries.

Allbutt (5), in 1895, associated arteriolar thickenings and cardiac hypertrophy as the results of the increased strain due to elevated blood pressure. Huchard (6), in France, independently developed a similar concept during this same period. These two men promoted the hypothesis that sclerosis of the vessels does not cause hypertension, but rather that hypertension causes the sclerosis.

At the same scientific meeting that the term "arteriosclerosis" was introduced by Marchand (7), in 1904, Romberg (8) presented a report in which he concluded that arteriosclerosis did not lead to any substantial increase in the blood pressure. The data on which his conclusions were based were obtained from measurements of the blood pressure of atherosclerotic patients made by Sawada (9). This announcement diverted attention to the problem of the interrelationships of hypertension and atherosclerosis.

Early in the experimental investigations of the relationships of these two pathologies, Klotz (10), in 1908, hung up rabbits by their

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hind legs for prolonged periods of time. He reported that, following this treatment, the rabbits developed lesions of the vessel walls resembling those observed in cases of human atherosclerosis. However, later investigators (11-13) were not able to reproduce these results. Anitschkow (14) concluded that the changes observed by Klotz were not due to elevated blood pressure. Saltykow (15) found various results in a number of additional experiments of this type which he reviewed in 1908.

Anitschkow (14) found, in 1914, that he could produce lipid deposits in the aorta of the rabbit by feeding cholesterin and prolonged compression of the abdominal aorta. He also observed that elevations of the blood pressure alone would not induce the lesions; whereas, cholesterin feeding alone was sufficient. His remarks on elevated blood pressure as a predisposing cause of the atherosclerotic condition were based upon his studies that an increase in the arterial blood pressure furthered the entrance and deposition of lipid in the wall of the blood vessels.

Through the 1920's Schmidtmann (16), Westphal (17), and Diecke (18) supported the theory that the elevation of the blood pressure, together with cholesterol, played an important part in the genesis of atherosclerosis. Later studies which appeared in the 1940's and 1950's strengthened this premise considerably. Wilens (19) repeated the work of Klotz (10) which had previously been discredited. He compared the development of aortic atheromatosis in cholesterol fed rabbits forced to sit upright for five hours a day with the lesions which developed in cholesterol fed control animals which were allowed to remain in a normal posture. In the sitting position, the rabbits developed an average elevation of the arterial blood pressure of 40 per cent above normal. This elevation reverted to normal when the animals were returned to their normal position. However, the animals with this temporary elevation of blood pressure developed more severe lesions, more rapidly than the control animals. Katz, Stamler, and Pick (20) demonstrated that chicks receiving desoxycorticosterone acetate, in addition to cholesterol, developed more atherosclerotic lesions than those fed cholesterol alone. Wakerlin and others (21), in 1951, demonstrated an acceleration of atherosclerosis in hypertensive, hypothyroid, cholesterol fed dogs. Bronte-Stewart and Heptinstall (22) produced a hypertensive condition first and then fed cholesterol to the rabbits in their experiments. Both groups demon-

strated comparable elevations of serum cholesterol. The hypertensive animals, however, had an average of 47 per cent aortic atheromata in contrast to only an 11 per cent average in the normotensive animals. A significant corollary to this observation is that, in the absence of cholesterol feeding, hypertension alone did not lead to the development of atherosclerotic lesions.

Tobian (23), in 1956, succeeded in inducing arteriosclerosis in rats by a combination of a high fat diet and artificially induced hypertension. Many additional references to experimental studies on this type of relationship have since appeared in the literature which reinforce the validity of the affiliation of these conditions.

With respect to the human, reports are appearing regularly in the literature which illustrate the association between hypertension and atherosclerosis. Rosenthal (24) showed that the fat content of the aorta paralleled the severity of atherosclerosis, and that the absolute values were higher in hypertensive individuals. Farber (25) made similar observations in hypertensive patients. Blackman (26) found that 86 per cent of hypertensive patients evidenced renal atherosclerosis in contrast to a 10 per cent occurrence in normotensive persons. Lisa, Eckstein, and Soloman (27) found a 60 to 43 per cent relationship. Richardson (28) reported that 75 per cent of the hypertensive patients, compared to 7 per cent of the normotensive individuals whom he examined, had renal atheromata. Tobian (23) commented that "In the vast majority of hypertensive patients, the essential hypertension comes first and then accelerates the formation of atheromata in the main renal arteries."

It is recognized that 85 per cent of coronary artery disease is atherosclerotic. Davis and Klainer (29) examined a large number of autopsies selected at random. They considered blood pressure readings taken prior to the terminal illness, and also sex and age. Only those persons with histories of systolic pressures greater than 150 mm Hg and diastolic pressures consistently above 90 mm Hg were classified hypertensive. An analysis revealed that 45 per cent of the hypertensive persons had severe coronary disease but only 27 per cent of the normotensive patients were so afflicted. Hypertensive women had marked coronary disease six times more frequently than normotensive females. A study by Master (30) revealed that men with hypertension are thirteen times more likely to develop myocardial infarction than normotensive males. Averbuck (31) found severe

coronary atherosclerosis, at necropsy, in 85 per cent of the cases with hypertension who died of cardiac failure.

A report by Hunter (32) demonstrated that blood pressures as little as 20 mm Hg lower than accepted "normal" values significantly increased the longevity of life expectancy.

Certain congenital cardiovascular defects indicate the hypertension-atherosclerosis relationship. For example, in patent ductus arteriosus with right to left shunt, or large interventricular septal defects, pulmonary arterial pressures quadruple their normal values (33). Individuals with such cardiovascular anomalies reveal at autopsy an extensive atherosclerosis of the pulmonary arterial tree but not of the systemic arteries. In coarctation of the aorta, the constriction in the descending thoracic aorta produces hypertension in the upper portions of the body but not below the constriction. As might be expected, there is more plaque formation in the region of the elevated blood pressure than below it. Once again, the fact that increased hydrostatic pressures directly influence the atherosclerotic process becomes evident.

Having briefly examined the clinical aspects of hypertension and atherosclerosis, it appears logical to inquire about the intrinsic causes of these diseases. The answer to this question must be secured before a rational and effective approach to therapy can be realized.

Many of the common denominators of these two diseases have been indicted and include such diversified influences as socio-economic, geographic, and other ecological factors. To this list have been added racial, personality, and sex characteristics. The former group vary considerably from generation to generation while the latter appear as hereditary components of the individual. Another particularly important hereditary characteristic is the peculiar "reaction to stress" which different individuals demonstrate. "Stress reactions" have been shown to have phylogenetically traceable linkage, and appear to exert a major influence in both hypertensive and atherosclerotic disease.

An examination of the historical background for the influence of heredity on these two pathologies revealed that this concept was by no means of recent origin.

The familial occurrence of "apoplexy" was reported as early as 1596 by Forestus (34). Morgagni (35), in 1761, Dewees (36), in

1833, and Dieulafoy (37), in 1875, published additional reports on the hereditary factor in cardiac pathologies.

More recent advances include the work of O'Hare, Walker, and Vickers (38) who published, in 1924, the first extensive study of heredity and hypertension performed in the United States. Their sample consisted of 300 unselected hypertensive individuals and 436 control patients having no apparent vascular disease. These authors concluded their report with the statement that "these cases of ours demonstrate rather conclusively that a family history of heart disease is almost twice as common in patients with hypertension as in ordinary patients with no increased blood pressure." Nador-Nikitits (39) discovered a similar situation in thirty-two hypertensives and their families which he traced back through three generations. Barach (40), in 1928, found that, in 95 per cent of individuals who suffered from hypertensive disease, there was a familial background of the condition.

Many investigators have added evidence for the genetic component of this malady through the years. Thomas and Cohen (41) reported, in 1955, that coronary artery disease was nearly four times as prevalent among siblings of individuals with coronary artery disease, as among the offspring of those parents apparently free from this disorder. In the same year, Pickering (42) proposed that life expectancy was inversely related to arterial pressure and that organic arterial disease and high blood pressure were closely correlated.

Referring to the work of Mendel (43) and Galton (44), Pickering (45), in 1957, re-evaluated the "genetic component" of hypertension. He compared the age-blood pressure levels of siblings and their parents. In both normotensive and hypertensive subjects, the rate of blood pressure rise with advancing age was the same, but the absolute values were significantly higher in the hypertensive group. The application of age adjustment factors to these estimates revealed that the slope of the scores of the siblings matched those of the parents. Pickering concluded from this regression analysis that essential hypertension was not the manifestation of a single gene inherited as a dominant or recessive factor. Rather, he proposed that this was a graded characteristic such as height and resulted from the effect of several polygenes. He allowed that his results were underestimated as to the size of this genetic factor, but it was not as large as the one for height.

With respect to genetic predisposing influences for atherosclerosis, an increasing accumulation of evidence tends to support this possibility. Since it is not yet established that hypercholesterolemia is not a component of atherosclerosis, genetic tendencies toward this condition are included in this discussion.

An analysis of 500 randomly selected patients who represented successive admissions to a general hospital was made by Schaefer and others (46). These results indicated hereditary hypercholesterolemia occurs in approximately 5.5 per cent of the population.

Adlersberg and his associates (47) investigated the incidence of idiopathic hypercholesterolemia in 200 randomly selected families in Staten Island, New York. Their findings showed that the occurrence of hypercholesterolemia was significantly greater among children of hypercholesterolemic parents than among the offspring of normocholesterolemic individuals. Adlersberg and Boas (48) proposed that hypercholesterolemia in primary xanthomatosis was an inborn error in metabolism which predisposed the individual to atherosclerosis. They stated that hypercholesterolemia represented a heterozygous abnormal state, while xanthoma was indicative of the homozygous abnormal situation. In short, there was an inherited malfunction in lipid metabolism, which paved the way for the onset of atherosclerosis. Wilkenson, Hand, and Fleigelman (49) studied familial hypercholesterolemia in four generations composed of 282 individuals and concluded that serum cholesterol elevations were "endogenous," not dietary and that the condition was inherited as an incomplete dominant trait.

Thomas (50) deduced that hypertension bore an etiological relationship to coronary artery disease. She stated that the heritage was expressed most often as hypertension in females and coronary artery disease in males. White (51) and McKusick (52) both emphasized that ". . . some genetic influence is involved in the pathogenesis of atherosclerosis including coronary heart disease." Additional supporting evidence of the role of heredity in hypercholesterolemic conditions and atherosclerosis was published by Adlersberg and others (53, 54).

Thomas and her associates (50) analyzed the prevalence of hypertension, coronary artery disease, obesity, and diabetes among students at Johns Hopkins Hospital. They found that, in the siblings of parents with a history of these conditions, hypertension occurred three

times, obesity four times, and diabetes eight times more frequently than these conditions occurred in normal parents and their children.

It has been postulated that the manner in which an individual reacts to stress is inherited and, therefore, the same stress stimuli do not produce identical effects in every person. This might account for the gradient distribution in the severity of hypertension and atherosclerosis found in different population samplings.

The biochemical results of stress have been presented by many authors (55-57). The two consequences of stress which contribute most to shortening life expectancy appear to be the elevation of the blood pressure and the alterations in the pathways of lipid metabolism.

Texon (58) recently applied some principles of fluid dynamics to the circulatory system and discovered that even slight alterations of vascular hemodynamics affected the progress of both hypertension and atherosclerosis.

Steinberg and Schafrir (59) reported that stress led to a hyperactivity of the adrenal gland and supra-normal excretion of epinephrine and nor-epinephrine. Both of these are pressor substances. They suggested an adrenal activity-hyperlipemia syndrome resulted from disturbing emotional experiences or stress. Dock (60) stated that "by augmentation of the adrenal cortical function, emotional stress caused an increase in sodium retention, a rise in blood pressure and serum cholesterol, and a decrease in the coagulation time." He also added that "high sodium chloride intake caused edema of the atheromatous plaques."

An attempt to appraise the significance of stress is exemplified by the study of Friedman and Rosenman (61). They studied three groups of men of comparable age and ethnic-socio-economic background. The difference in these groups was a tendency to compete, meet deadlines, and drive toward attainment of goals. These features were present to a high degree in the first group and completely lacking in the second. A third group served as controls and consisted of blind men, unemployed, suffering from financial and physical insecurity, and manifesting a chronic state of anxiety. The results showed that the first group had higher serum cholesterol levels and that heart disease occurred in this group seven times more frequently than in either of the others. These authors suggested that this pattern is on the increase and will soon become ubiquitous with the increased stresses of modern living.

Ethnic influences of a hereditary nature have been implicated by numerous investigators who place emphasis on the epidemiological aspects of this problem. Ethnic, geographic, and socio-economic influences in the past were easily analyzed. Today the situation is changed since there is less tendency for particular groups to remain in one geographic area for generations.

Scant information appeared before 1900 with respect to this aspect of the problem. Allbutt (62) expressed the degree of influence that these factors might exert on the hypertension-atherosclerosis problem when he wrote: "Of Race, Country and Climate in respect to Arteriosclerosis we know little and this little suggests that these factors are at most of subordinate importance." As late as 1931, White's text on heart disease (63) dismissed hypertension with the brief remark: "It was less severe in tropical climates and uncommon in Chinese." For the past thirty years, investigators have presented conflicting evidence on this problem. For example, Alaskan Eskimos were reported to suffer from atherosclerosis but not hypertension (64). On the other hand, Hawaiian plantation workers were commonly afflicted with both hypertension and atherosclerosis (65). Kirghiz nomads have been observed to be susceptible to both atherosclerosis and Bright's disease (66). Snapper (67) reported hypertension but little atherosclerosis in poor Chinese.

A more recent study was made by Stamler and his associates (68) on the serum cholesterol levels of middle aged Caucasian males compared to the serum cholesterol levels of middle aged Negro men in the same environment. The results revealed that the Negro men had significantly lower serum cholesterol levels. The authors inferred that this explained a paradox among the Negro population. It appears that Negroes have a greater incidence of hypertension morbidity and a mortality rate five times greater than that of the white population from this condition. However, the incidence of atherosclerosis is not significantly higher in Negroes.

The occurrence of atherosclerosis alone, without associated hypertension, is common in some ethnic groups. In the United States, this is not necessarily the case.

Another factor which has been related to both hypertension and atherosclerosis is obesity. This condition is accused of being a contributing factor.

Master, Jaffee, and Chesky (69) indicated the harmful influence of obesity on both the normal and the hypertensive and atherosclerotic conditions. Life insurance and other studies including the four-year study recently completed by Lew (70) showed consistently that, in overweight persons, there was a significantly higher incidence of both hypertension and atherosclerosis than in persons of normal weight. Pell and Alonzo (71) estimated that obesity increased the risk of myocardial infarction by fifty per cent. When both obesity and hypertension are present, the risk of an infarction is three and one-half times greater than in a normal patient. There is the possibility that obesity is a type of "response to stress" in certain individuals. Experiments in animals have shown that endocrine disturbances and other modifications which favor obesity have influenced atherosclerosis positively.

Thomas and her associates (72) reported no correlation between serum cholesterol levels and body weight. This does not mean that the adverse effects of obesity are to be discounted.

A number of recent reports relate tobacco smoking to atherosclerosis and hypertension. A study in Finland by Karvonen *et al.* (73) showed that smokers had higher serum cholesterol levels and lower blood pressure levels than non-smokers. Thomas and Murphy (74) conducted a similar study in the United States and confirmed these findings. In relation to atherosclerosis, it appears that blood pressure is a more important factor than smoking.

Therapeutic approaches to decrease this combination of morbidities have, in the past, been directed toward the reduction of each condition separately. Attempts were made to lower serum cholesterol levels by diets and therapeutic agents in an effort to diminish the severity of the atherosclerotic condition. Other investigators considered the problem of elevated blood pressure as more important and emphasized the desirability of reducing the blood pressure to normal levels. Both of these approaches demonstrated some degree of success but there was still much to be desired.

Several investigators happened to examine the blood chemistry of patients being treated with various tranquilizing agents. They found that these agents, in certain instances, markedly lowered the serum cholesterol levels in both normal and hypertensive patients.

In 1953, a report by Schroeder (75) mentioned that hypertensive patients treated with a combination of hydralazine and hexamethonium

exhibited ". . . a tendency for the serum cholesterol to decrease." Since serum cholesterol levels were generally accepted as an indicator of atherosclerotic tendencies, it appeared that a therapeutic approach had been found which might cope simultaneously with both horns of this pathological dilemma.

Orvis and others (76) explored the coincident changes in serum cholesterol levels of hypertensive patients treated with pentolinium, mecamylamine, and chlorisondamine. Their results showed that patients treated with pentolinium had a decrease in blood pressure, as might be expected, but also experienced a decrease in the serum cholesterol level to an average of 57.8 milligram per cent less than their mean pretreatment level. In other hypertensive individuals, mecamylamine and chlorisondamine produced a 26 per cent reduction from pretreatment serum cholesterol levels. In all three groups, it was observed that the administration of the drug produced greater reductions of blood cholesterol levels in hypercholesterolemic patients than in normal individuals.

Corcoran and his associates (77) reported on their experiences with the use of antihypertensive drugs in atherosclerotic complications in 1956. Following the lead of these studies, Hollister (78) investigated chloropromazine and the adrenergic blocking agents, phenoxybenzamine, pentolamine, and HYDERGINE (a combination of equal parts of the methane sulfonate derivatives of dihydroergocornine, dihydroergocristine, and dihydroergokryptine). In his experimental design, he chose to consider as a significant change a reduction of 25 per cent from the mean control value before treatment. His experimental group consisted of 13 patients. The results of this study tended to indicate that these agents had an ability to reduce elevated serum cholesterol levels. Hollister explained that the purpose of these investigations was to investigate the possibility that adrenergic blockade might have an effect in the neuro-humoral mechanisms associated with the control of lipid metabolism. The agents he employed all shared the common property of being adrenergic-blocking substances.

Somoza (79), in 1958, found that reserpine decreased elevated serum cholesterol levels and the severity of atherosclerotic lesions in rabbits. Similar findings were not reported by Krag and his coworkers (80), who observed in humans, no alterations of serum cholesterol or serum lipoproteins resulting from the administration of reserpine over a one-year period.

An examination of the recent literature reveals that many clinicians are presently selecting "antihypertensive" agents for use in the treatment of atherosclerosis. The reason for this trend appears to be the increasing emphasis upon the importance of blood pressure levels in the pathogenesis of cardiovascular diseases, especially atherosclerosis.

In these reports, tranquilizers and diuretics are considered with specific "antihypertensive agents." While the pharmacological mechanisms of these agents are separate and distinct, the effects which they produce are beneficial and appear to justify their continued use. In the light of the many reports about the manner in which emotional factors are involved in the genesis of this pathology, it seems necessary that these agents be appraised more thoroughly. The primary site of action or mechanisms by which they act against the atherogenic process has yet to be exactly determined.

Summary

From the presently available information, it appears that hypertension and atherosclerosis share many hereditary and non-hereditary origins. While it is possible to have either disease separately, the presence of one often indicates or predicts the onset of the other. Their insidious combination, which drastically reduces life expectancy, is being reported with increasing frequency in the United States each year. In view of these established facts, the possibility of reducing both elevated serum cholesterol and elevated blood pressure simultaneously is deserving of further investigation. Additional clinical and experimental studies are still required before a final solution to this perplexing problem will be realized.

REFERENCES

(1) Harvey, Wm., *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus.* Fitzerus, Frankfort (1628).

(2) Traube, L., *Ges. Beitr. s. Pathol. u Physiol., 2:*290 (1871).

(3) Kirkes, W. S., *Medical Times and Gazette, 15:*109 (1857).

(4) Gull, Wm., and Sutton, H., *Med. Chir. Trans., 55:*273 (1872).

(5) Allbutt, T. C., *Trans. Hunterian Soc., 3:*38 (1895).

(6) Huchard, H., *Les maladies de'l Hypertension arterielle,* Paris (1904).

(7) Marchand, F., "Über Arteriosklerose (Atherosklerose)," *Verhandl. Kongress inn. Med., 21st Kongress,* Leipzig (1904).

(8) Romberg, E., "Über Arteriosklerose," *ibid.*

(9) Sawada, K., *Deut. med. Wochschr., 30:*425 (1904).

(10) Klotz, O., *Centr. f allgem. Pathol. u Patholc. Anat., 19:*535 (1908).

(11) Fahr, Th., *Verhandl. d. deut. pathol. Ges., 13:*162 (1909).

(12) Starokadomsky, L., and Ssoblew, L. W., *Frankfur. Z. Pathol., 3:*912 (1909).

(13) Steinbliss, W., *Virchow's Arch. pathol. Anat. u Physiol., 212:*152 (1913).

(14) Anitschkow, N., *Beitr. pathol. Anat. u. allegm. Pathol., 59:*306 (1914).

(15) Saltykow, S., *ibid., 43:*147 (1908).

(16) Schmidtmann, M., *Virchow's Arch. pathol. Anat. u Physiol., 181:*363 (1922).

(17) Westphal, K., *Z. klin. Med., 101:*56 (1925).

(18) Deicke, O., *Krankheitsforsch., 3:*399 (1926).

(19) Wilens, S. L., *Am. J. Path., 19:*293 (1943).

(20) Katz, L. N., Stamler, J., and Pick, R., *Nutrition and Atherosclerosis,* Lea and Febiger, Philadelphia (1958).

(21) Wakerlin, G. E., Moss, W. G., Neville, J. B., and Bourque, J. E., "The Effect of Experimental Renal Hypertension on Experimental Cholesterol Atherosclerosis," in *Factors Regulating Blood Pressure; Transactions of the Fifth Conference,* Josiah Macy Foundation, New York (1951).

(22) Bronte-Stewart, B., and Heptinstall, R. H., *J. Pathol. Bact., 68:*407 (1954).

(23) Tobian, L., "Hypertension and Atherosclerosis," in *Symposium on Atherosclerosis.* University of Minnesota Press, Minneapolis (1956).

(24) Rosenthal, S. R., *A. M. A. Arch. Pathol., 18:*660 (1934).

(25) Faber, M., *Acta Med. Scand., 125:*418 (1946).

(26) Blackman, S. J., *Bull. Johns Hopkins Hosp., 65:*353 (1939).

(27) Lisa, J. R., Eckstein, D., and Soloman, C., *Am. J. Med. Sci., 205:*703 (1943).

(28) Richardson, G. O., *J. Pathol. Bact., 55:33* (1943).

(29) Davis, D., and Klainer, M. J., *Am. Heart J., 19:*185 (1940).

(30) Master, A., *Circulation, 8:*170 (1953).

(31) Averbuck, S. H., *Am. Heart J., 11:*99 (1936).

(32) Hunter, A., *J. Inst. Actuaries, 70:*60 (1939).

(33) Williams, G. D., "Hereditary Aspects of Arterial Hypertension in Relation to Arteriosclerosis," in *Arteriosclerosis (Cowdry),* Macmillan, New York (1933).

(34) Forestus, P., *De Rerum Affectibus ac Morbis,* Lugdini, Plantiniana (1596).

(35) Morgagni, G. B., *De sedibus et causis morborium per anatomen indignatis,* Venice (1761).

(36) Dewees, W. P., *Practice of Physic,* Carey, Lea and Blanchard, Philadelphia (1833).

(37) Dieulafoy, G., *Des progress realises par la physiologie experimentale dans la connaissance des maladies du systeme nerveux,* Paris (1875).

(38) O'Hare, J. P., Walker, W. G., and Vickers, M. C., *J. Am. Med. Assoc., 83:27* (1924).

(39) Nador-Nikitis, E., *Arch. maladies coeur et vaisseaux, 18:*582 (1925).

(40) Barach, J. H., *J. Am. Med. Assoc., 91:*1511 (1928).

(41) Thomas, C. B., and Cohen, H. B., *Ann. Int. Med., 42:*90 (1955).

(42) Pickering, G. W., *High Blood Pressure,* Churchill, London (1955).

(43) Mendel, G. J., *Verhandl. naturforsch. Ver. Brünn, 4:*3 (1866).

(44) Galton, F., *Inquiries Into Human Faculty and Its Development,* London (1883).

(45) Pickering, G. W., *Triangle, 3:*59 (1957).

(46) Schaefer, L. E., Drachman, S. R., Steinberg, A. G., and Wang, G. I., *Am. Heart J., 46:*99 (1953).

(47) Adlersberg, D., Schaefer, L. E., Steinberg, A. G., and Wang, G. I., *Circulation, 10:*600 (1954).

(48) Adlersberg, D., and Boas, E. P., *J. Mt. Sinai Hosp., 12:*84 (1945).

(49) Wilkinson, C. F., Jr., Hand, E. A., and Fliegelman, M. T., *Ann. Int. Med., 29:*676 (1948).

(50) Thomas, C. B., *Am. J. Med. Sci., 224:*367 (1952).

(51) White, P. D., *New England J. Med., 256:*965 (1957).

(52) McKusick, V. A., *Eugenics Quart., 5:*30 (1958).

(53) Adlersberg, D., Parets, A. D., and Boas, E. P., *J. Am. Med. Assoc., 141:*246 (1949).

(54) Adlersberg, D., Schaefer, L. E., and Drachman, S. R., *J. of Lab. Clin. Med., 39:237* (1952).

(55) Selye, H., *The Physiology and Pathology of Exposure to Stress,* Acta Inc., Medical Publishers, Montreal (1950).

(56) Wertlake, P. T., Wilcox, A. A., Haley, M. I., and Peterson, J. E., *Proc. Soc. Exp. Biol. Med., 97:*163 (1958).

(57) Grundy, S. M., and Griffin, A. C., *Circulation, 19:*496 (1959).

(58) Texon, M., *Am. J. of Cardiol., 5:*291 (1960).

(59) Steinberg, D., and Shafrir, E., National Heart Institute News Release, May (1960).

(60) Dock, Wm., *Heart Bull., 8:73* (1959).

(61) Friedman, M., and Rosenman, R. H., *Canad. Med. Assoc. J., 81:*195 (1959).

(62) Allbutt, C., *Diseases of the Arteries,* Macmillan, London (1915).

(63) White, P. D., *Heart Disease,* Macmillan, New York (1931).

(64) Rodahl, K., *Norsk Polarinstitutt Skrifter Nr. 102,* Oslo (1954).

(65) Larsen, N. P., *Am. Practitioner Dig. of Treatment, 6:*1681 (1955).

(66) Kuczynski, B., *Klin. Wochschr., 4:*39 (1925).

(67) Snapper, I., *Chinese Lessons to Western Medicine,* Interscience, New York (1941).

(68) Stamler, J., Lindenberg, H. A., Berkson, D. M., Miller, W. A., and Paganin, M., "A Comparison of the Serum Cholesterol Levels in Middle-aged Caucasian and Negro Men," 13th Annual Meeting, *Am. Soc. for the Study of Arteriosclerosis,* Chicago (1959).

(69) Master, A. M., Dack, S., and Jaffe, H. L., *Arch. Int. Med., 64:*767 (1939).

(70) Lew, S., *Statistical Bull. Metropolitan Life Insurance Co., 41:*1 (1960).

(71) Pell, S., and Alonzo, C. A., *J. Am. Med. Assoc., 166:*322 (1958).

(72) Thomas, C. B., and Cohen, B. H., *Ann. Int. Med., 42:*90 (1955).

(73) Karvonen, M., Orma, E., Keyes, A., Brozek, J., and Fidanza, F., *Lancet,* Mar. 7, 492 (1959).

(74) Thomas, C. B., and Murphy, E. A., *Ann. Int. Med., 50:*970 (1959).

(75) Schroeder, H. A., *Hypertensive Disease,* Lea and Febiger, Philadelphia (1955).

(76) Orvis, H. H., Tamanga, I. G., and Evans, J. M., *Circulation, 17:*176 (1958).

(77) Corcoran, A. C., Page, I. H., Dustan, H. R., and Lewis, L. A., *Cleveland Clin. Quart., 23:*115 (1956).

(78) Hollister, L. E., *J. Chronic Dis., 6:*234 (1957).

(79) Somoza, C., *Proc. Soc. Exp. Biol. Med., 99:*347 (1958).

(80) Krag, C. L., Strisower, E. N., Green, H. R., Strisower, B., Gofman, J. W., and Galioni, E. F., *Internat. Rec. Med., 171:*11 (1958).

SELECTED ABSTRACTS

The Antibacterial Effect of Chlorobutanol. Anderson, R. A., and Stock, B. H. *Australasian J. Pharm. 41*:556 (1960). The antibacterial effect of chlorobutanol on *Micrococcus Pyogenes* var. *aureus* B313 was studied using a technique which determined the rate of kill. A standardized broth culture of the test organism was added to the chlorobutanol solutions in the ratio of 0.02 ml. of culture to 20 ml. of solution. After 6, 12, 18, 24, 30, and 40 minutes, suitable samples of the contaminated chlorobutanol solutions were mixed with sterile water on the surface of dried agar plates and then incubated. The size of the samples varied from 0.02 ml. to 0.5 ml. in order to give as close to 100 organisms per plate as possible.

It was found that the activity of chlorobutanol was greater at a pH of 5.0 than at higher pH values. Therefore, the chlorobutanol solutions were prepared in a M/40 phthalate buffer at a pH of 5.0.

Using three different concentrations of chlorobutanol, at a controlled temperature of 24°C., it was found that the concentration employed is significant. With a 0.25 per cent concentration, it was found that there was antibacterial activity but, even after 40 minutes, there were approximately 2.7 per cent survivors. With a 0.4 per cent concentration, there were only 0.1 per cent survivors after 30 minutes but, with a 0.5 per cent solution, there were no survivors after 24 and 30 minutes. The authors warned, therefore, that reduced concentrations due to loss by hydrolysis or other reasons may render the chlorobutanol ineffective as an antibacterial in the preparation in which it is employed.

It was also found that temperature has a pronounced effect on the rate of kill of the test organism. Using a 0.4 per cent solution of chlorobutanol, there were no survivors after 18 minutes at a temperature of 30°C. but there were about 5 per cent survivors after 24 minutes at a temperature of 20°C. Although no test results were recorded, the authors indicated that propylene glycol seemed to increase the activity of chlorobutanol.

Side Effects From Propionyl Erythromycin. Kuder, H. V. *Clin. Pharmacol. and Therapeutics 1*:604 (1960). Propionyl erythromycin and its lauryl sulfate salt produce higher and more sustained blood levels of antibacterial activity following oral administration than does erythromycin in comparable doses. The report given here surveyed the side effects associated with the use of these preparations in 20,525 patients. The therapeutic results were not reported in detail but the expected therapeutic effectiveness was obtained.

No cases of serious side effects or toxicity were reported. Of the 9,558 patients who received propionyl erythromycin, 5.7 per cent had gastrointestinal side effects. An additional 1.1 per cent had other side effects, including cutaneous eruptions, urticaria, and miscellaneous manifestations. The drug was discontinued in 0.7 per cent of the patients in this group because of side effects.

The majority of the 10,967 patients given propionyl erythromycin lauryl sulfate were children; 1,933 were less than two years of age. Gastrointestinal side effects were noted in 2.0 per cent of these patients. An additional 0.5 per cent had other side reactions, including cutaneous eruptions and urticaria. The drug was discontinued because of side effects in 0.4 per cent of the patients treated.

The author concluded that the administration of propionyl erythromycin and propionyl erythromycin lauryl sulfate will result in no more frequent and possibly less frequent side effects than have been previously reported from the parent substance, erythromycin.

Preoperative Medication With Atropine. Joseph, M. C., and Vale, R. J. *The Lancet* No. 7159:1060 (1960). The use of oral atropine in comparison with subcutaneous atropine for preoperative medication was studied by the authors in 147 children. The children ranged in age from 3 to 12 years and averaged about 6½ years. They were admitted for tonsillectomy and were under the care of the same surgeon and anesthetist. The average interval between administration of atropine and induction of anesthesia was 95 and 87 minutes for the oral and subcutaneous groups, respectively. The dose of atropine was 0.85 mg. by mouth or 0.64 mg. subcutaneously. The effects were based upon the degree of salivation at the time of operation, the size of the pupils, and the pulse rate.

It was found that there was no appreciable difference between the effects of atropine when given by mouth and when given subcutaneously as preoperative medication. There was a marked decrease in salivation in 63 of 74 patients following oral medication and in 68 of 73 following subcutaneous medication. The decrease in salivation was the best method of evaluation. The average size of the pupils was identical in the two groups and the incidence of negative reaction to light was similar. The pulse rate rose 22 following atropine in the oral group and 25 in the subcutaneous group.

The authors concluded that, since there was no significant difference in response in the two groups, atropine should be given orally as preoperative medication, especially in children.

The Interaction of Tweens With Certain Pharmaceuticals. Ahsan, S. S., and Blaug, S. M. *Drug Standards 28*:95 (1960). The high molecular weight polymers falling into the general category of polyethers have found increasing use in pharmaceutical and cosmetic formulations. Although these compounds are usually chemically inert, they often appear to react with small molecules to form complexes that may be soluble or insoluble in aqueous systems. Such complexes may influence the solubility, stability, and pharmacologic activity of the pharmaceutical compounds which constitute a part of the complex.

The authors studied the complexing tendencies of Tweens differing in the fatty acid content of the molecule, including the monolaurate, monopalmitate, monooleate, and monostearate, with certain pharmaceuticals. The complexing tendency was evaluated on the basis of the solubility of the complex formed. If a complex is formed, an increase or a decrease in the solubility of the pharmaceutical is noted, depending upon the nature of the complex formed.

With phenobarbital, all of the Tweens showed an increase in solubility at a Tween concentration of 1.2 per cent. The greatest increase was obtained with Tween 60 showing a 245 per cent increase in solubility. Aspirin showed the highest increase also with Tween 60, it being 129 per cent. Boric acid showed no increase or decrease in solubility with the Tweens. Ortho-hydroxybenzoic acid showed an increase with all of the Tweens, the greatest being 192 per cent with

Tween 80. Para-hydroxybenzoic acid also showed an increase with all of the Tweens, the highest being 127 per cent with Tween 40. However, *m*-hydroxybenzoic acid showed no increase or decrease in solubility, thus indicating that complexation had not occurred. The authors also stated that the extent to which the above complexing occurred with the Tweens was considerably greater than that reported previously with polyethylene glycols. It was concluded that the presence of the non-polar moiety in the Tweens increased the degree of complexation. Both phenol and resorcinol formed water-insoluble oily liquids with the Tweens.

Evaluation of Studies on an Attenuated Measles Virus Vaccine. Katz, S. L., *et al. New England J. Med. 263:*180 (1960). This report summarized the findings on the use of an attenuated measles virus vaccine reported in other papers of the series.

A total of 303 children received the vaccine—272 by the parenteral route (usually subcutaneous) and 31 by the oral, intranasal, or conjunctival route. A serologic response to the vaccine was obtained in 60.7 per cent of the children, representing 96.5 per cent of the 171 children having no demonstrable antibodies initially. Children having pre-existing antibodies showed no clinical or serologic response to the vaccine. The vaccine was shown to produce a highly effective protection against measles in a closed environment. There was no evidence of spread of the vaccine virus from recipients to susceptible contacts.

There was no local reaction to parenteral inoculation of the vaccine. Clinical reaction of 171 children without initial antibodies consisted principally of fever (83 per cent) and a modified rash (48 per cent). Koplik spots were detected in only 16 per cent of the children examined. There were no febrile seizures. There was also an absence of catarrhal signs.

It was concluded that clinical trials of the attenuated measles virus vaccine should be extended conservatively. Parents must be made aware of the dangers from ordinary measles but also of the anticipated reactions to the vaccine. Meanwhile, every effort should be made to provide a vaccine that will induce comparable serologic response with less febrile reaction.

Corticosteroid Therapy of Ulcerative Colitis. Truelove, S. C. *Brit. Med. J. 1*:464 (1960). The author reported the results of a study to determine the relative effectiveness of several corticosteroid treatments for mild or moderately severe ulcerative colitis. It was found that 35 per cent of the 40 patients given only prednisolone orally in a dose of 5 mg. each night showed a rapid remission of the ulcerative colitis. In a group of 20 patients given 100 mg. of hydrocortisone hemisuccinate sodium each night by rectal drip, 70 per cent showed a complete remission from symptoms. In another group of 20 patients given 40 mg. of prednisolone 21-phosphate each night by rectal drip, the remission rate was 75 per cent. A combination of oral prednisolone and nightly rectal drip of prednisolone 21-phosphate did not improve the remission rate. However, the combination of oral prednisolone with the nightly drip of hydrocortisone hemisuccinate sodium brought about a rapid remission of all symptoms in all 20 patients treated. While this result was obtained within two weeks, the author did not recommend that therapy be discontinued after only two weeks. Continued treatment for several weeks appeared to reduce the likelihood of a recurrent attack.

A Study of the Stability of Atropine Solutions. Lu, F. C., and Hummel, B. C. W. *J. Pharm. and Pharmacol. 12*:698 (1960). An evaluation of the stability of solutions of atropine was undertaken by the authors with both chemical and biological assays being performed. Samples of five lots of atropine tartrate solution and two lots of atropine sulfate solution of commercial origin were studied. These varied in age from about 2 years to 6 years. In addition, two lots of partially hydrolyzed atropine sulfate solution were prepared.

The solutions were assayed biologically on isolated guinea pig ileum. The contractions of this section of intestine were induced by acetylcholine and the magnitude of the contractions compared before and after a dose of the atropine solutions. It was found that there was a definite inverse relation between the strength of the sample and the duration of storage. The sample that was two years old had lost about 13 per cent of its strength and the sample that was six years old had lost about 26 per cent of its strength. These results were compared with the results obtained using the Vitali-Morin spectrophotometric assay. There was no significant difference in the

results obtained using the biological and the chemical methods of assay.

The authors also evaluated the spasmolytic and lethal activity of the partially hydrolyzed atropine sulfate solution in order to determine whether or not aged samples would increase in either of these activities in proportion to the other. This was to determine whether or not the products of hydrolysis were more toxic than the unhydrolyzed drug. It was found that there was a slight and practically equal increase in both of these activities as compared with the known content of unhydrolyzed atropine sulfate. The hydrolysis products apparently increased the biological activity slightly but without undue augmentation of either. Therefore, it would appear that the hydrolysis products of atropine are not significantly more toxic than unhydrolyzed atropine.

The findings from this study would indicate that either chemical or biological assay methods may be used for the evaluation of the stability of solutions of salts of atropine. It would also appear that a solution that was six years old would have lost about 25 per cent of its activity but that the products of hydrolysis would not be more toxic than the drug.

The Toxicity of Estrogens on the Liver. Kulcsár-Gergely, J., and Kulcsár, A. *J. Pharm. and Pharmacol. 12*:312 (1960). Lesions were induced in healthy mature rats by the administration of carbon tetrachloride. One group of animals were given estrogens and another group remained untreated as controls. In another series of studies, mature ovariectomized rats were similarly treated.

The authors found that the damaged liver quickly lost its ability to inactivate estrogen. After hepatic damage, it was found that the level of endogenous estrogen rose significantly. With this rise, there was evidence of deterioration in the condition of the damaged liver. When ovariectomized animals were given estrogen in large doses (loaded), the condition of the damaged liver also deteriorated. This indicated that loading the animal with estrogen increased the strain on the damaged liver, probably because of its reduced inactivating capacity, and caused further deterioration.

A comparison of clinical data reported in the literature with the results from these studies led the authors to conclude that estrogen therapy is contra-indicated in cases where hepatic damage is present.

BOOK NOTICES AND REVIEWS

Drugs of Choice, 1960-1961. Walter Modell, Ed. The C. V. Mosby Co., St. Louis, Missouri, 1960. Price: $13.50.

This book, the second edition of Dr. Modell's *Drugs of Choice,* provides to the medical profession an authoritative and unbiased source of information on the choice of a particular drug for a particular clinical situation. The material in this text is presented in a manner which is both complete and concise and, thus, enables the practicing physician to quickly select the proper drug for the particular condition he is treating.

Each chapter of this book deals with the use of drugs according to pharmacologic acion. Within the body of each chapter is a discussion of the general pathology of the diseases being treated, the theory of a specific treatment, and the drugs to be used, including indications, possible modes and sites of action, posology, contraindications and side effects. Appended to the text is a Drug Index, arranged alphabetically by both generic and trade name, which presents the manufacturer, method of administration, and available dosage forms of each product.

This book is well-written and easily read, and, although primarily intended for the clinician, it will serve as an excellent reference for those engaged in medical research.

E. E. VOGIN

Einführung in die Pharmakopsychologie by Dr. Med. et Phil. Herbert Lippert. Volume 4 of the "Enzyklopädie der Psychologie in Einzeldarstellungen." 256 pp. Editor—Professor Dr. phil. Robert Heiss; publisher—Hans Huber, Bern and Stuttgart, 1959. Price: about $8.00.

This is an introduction into the field of pharmacopsychology which brings the psychological aspect of pharmacology into the proper perspective of drug action.

Pharmaceutical Pocket Book 1960. 17th Edition, published by the direction of the Council of the Pharmaceutical Society of Great Britain. London, The Pharmaceutical Press, May 11, 1960.

A handy reference book for the practicing pharmacist giving information on varied subjects.

Fundamentals of Physical Chemistry. H. D. Crockford and Samuel B. Knight. xvii + 463 pp. John Wiley & Sons, Inc., New York, N. Y., 1959. Price: $6.95.

This book is based on a book published in 1950 under the title *Fundamentals of Physical Chemistry for Premedical Students.* It has been written for students with the usual undergraduate background in general chemistry, qualitative analysis, and quantitative analysis. Several new topics are presented; these include the change in the value of the equilibrium constant with temperature, the change of vapor pressure with temperature, and the energy of activation in reaction kinetics. The chapter on radiochemistry includes a thorough treatment of this research tool. Three new chapters on thermodynamics have been introduced in such a way that they may be used any time in the course.

A modern treatment of the subject matter has been employed. A set of review questions to provide proper emphasis for the important topics is given at the end of each chapter. All sections, equations, tables, and figures are numbered in such a way to make cross reference easy. Although the coverage of topics is extensive, it does not go into a complete treatment of each topic.

The Operation of Sterilising Autoclaves, A Symposium held at Brighton Technical College, School of Pharmacy. 45 pp. The Pharmaceutical Press, 17 Bloomsbury Square, London, 1959. Price: 7s. 6d.

This symposium is devoted to the principles of steam sterilization and the methods of testing the bactericidal efficiency of steam sterilization, as well as the operation and use of sterilizing equipment.

Lipide Metabolism. Edited by Konrad Bloch. xiii + 411 pp. John Wiley & Sons, Inc., New York, N. Y., 1960. Price: $10.50.

This book, planned as a companion to Hanahan's *Lipide Chemistry*, is a series of contributions dealing with the transformations of lipides by living systems and by isolated enzymes. Included are chapters on the chemistry and immunochemistry of bacterial lipides and on hormonal and other mechanisms which control the transformation of lipides.

Each of the eight chapters, written by an authority in the field, includes extensive references.

Released Mental Patients on Tranquilizing Drugs and the Public Health Nurse. Ida Gelber. xiii + 139 pp. New York University Press, 1959. Price: $3.00.

This publication is the first in a series of nursing research monographs designed to present significant investigations carried out in the Department of Nursing Education at New York University.

Drugs and Behavior. Edited by Leonard Uhr and James G. Miller. xix + 676 pp. John Wiley & Sons, Inc., New York, N. Y., 1960. Price: $10.75.

This book is in a sense a "progress report" on the search for more precise experimental methods in the delineation of the behavioral toxicity, therapeutic effects, and actions of psychoactive drugs. Chapters are included which discuss general theoretical and methodological issues involved in drug research and those reporting on specific researches conducted by the contributors. In addition, several articles suggest and describe new methods and techniques which promise to be of value in future psychopharmacological research.

The general index offers a brief description of the action and known effect of each drug mentioned in the book.

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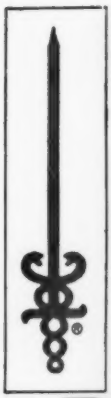

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